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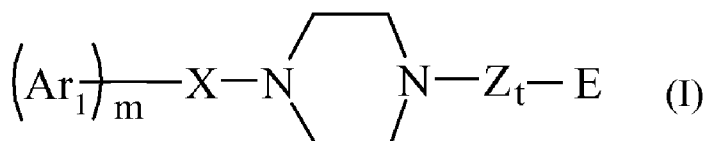
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(54) Title: PIPERAZINES DERIVATIVES AS PROTEASOME MODULATORS



(57) Abstract: The instant invention relates to the use of at least one piperazine derivative of formula (I); or a pharmaceutically acceptable salt thereof, as proteasome activity modulator for the preparation of a pharmaceutical composition intended to prevent and/or treat a disease condition mediated by the proteasome activity.



### Piperazine derivatives as proteasome modulators

The present invention relates to the identification and the use of piperazine derivatives as modulators of proteasome activity. More particularly, the invention relates to the use of piperazine derivatives for the preparation of pharmaceutical compositions or in  
5 cosmetic compositions. The present invention is also directed to a method of prevention and/or treatment of disease conditions mediated by proteasome activity, in particular cancer conditions, comprising the administration of piperazine derivatives in accordance with the invention.

In eukaryotes, the non-lysosomal protein degradation is mainly performed by  
10 the strictly controlled complex enzymatic machinery of the ubiquitin–proteasome pathway. Proteasomes are involved in protein quality control and turnover of many critical proteins participating in a vast number of essential biological processes, such as signal transduction, cell proliferation, cell cycle control, cell differentiation and apoptosis (Coux *et al.*, *Annu Rev Biochem* 1996, 65, 801; Ciechanover *et al.*, *Proc Natl Acad Sci U S A* 1998, 95:2727).

15 The 26S proteasome is formed by the 20S catalytic core, capped at each end by a regulatory component termed the 19S complex, responsible in part for the selective degradation of a given substrate.

The 20S proteasome core particle is composed of 28 subunits that are arranged into four stacked rings of seven  $\alpha$ -type subunits or seven  $\beta$ -type subunits.

20 The central proteolytic chamber of this endoprotease is composed of the two  $\beta$ -rings. Each  $\beta$ -ring has three different proteolytic activities associated to a N-terminal threonine hydrolase, referred to as chymotrypsin-like (CT-L), post glutamyl peptide hydrolysing or post-acid (PGPH or PA) and trypsin-like (T-L).

Because the proteasome is a universal and broadly active cellular component, it  
25 is not surprising that it has been proposed as an interesting target in many disease indications. For instance, the proteasome plays a key role in immune surveillance against virus and cancer, because it is involved in antigen processing and presentation to cytotoxic T cells, and in activation of nuclear factor-kappa B that is the central transcription factor of the immune system. It plays also a role in inflammatory responses, such as inflammatory  
30 arthritis, muscle atrophy, in several dystrophies such as limb-girdle muscular dystrophy (LGMD-1C) and Duchenne muscular dystrophy (DMD), as well as sleeping sickness.

The proteasome is also proposed as target for cancer therapy, as cancer cells are more susceptible to undergo apoptosis than normal cells after treatment with proteasome inhibitors (Adams *et al.*, *Cancer Cell*, 2004, 5:417). Proteasome inhibitors sensitize cancer cells and tumours to the proapoptotic effects of conventional  
5 chemotherapeutics and radiation therapy (Yu *et al.*, *Mol Cancer Ther*, 2006, 5:2378).

Several classes of proteasome inhibitors have been described, most of these inhibitors are peptidic derivatives or natural compounds, but the large majority of these molecules is bearing a reactive group and act as covalent inhibitors. Typically, proteasome inhibitors are sorted according to their ability to interact covalently or non-covalently with  
10 the active sites of the proteasome. The different classes of proteasome inhibitors are reviewed by Borissenko & Groll (*Chemical Rev.*, 2007, 107:687) and Papapostolou & Reboud-Ravaux, (*J Soc Biol*, 2004, 198:263).

For example, Velcade<sup>®</sup> or bortezomid, which is the first proteasome inhibitor approved by the FDA, is a covalently interacting proteasome inhibitor. This compound is a  
15 dipeptide boronic acid which is sensitive to oxidation (Pekol *et al.*, *Drug Metab Dispos*, 2005, 33:771). The natural compound TMC-95 is a non-covalently interacting proteasome inhibitor (Kohn *et al.*, *J Org Chem*, 2000, 65:990). However, this compound presents the drawbacks of having a very complex structure, rendering complicated its synthesis, and a high molecular weight, conferring to it a weak bioavailability.

20 On the other side, proteasome activators may be useful for disease conditions mediated by accumulation of proteins or polypeptides.

For example, the activation of proteasome should accelerate and improve the intracellular proteolysis favoring the removing of oxidized protein associated with aging, in particular skin aging. Proteasome activators would also be helpful in disease conditions  
25 associated with proteins accumulation such as Alzheimer disease or Parkinson disease.

Proteasome activators are, for example, described in Kisselev *et al.*, (*J. Biol. Chem.* 2002, 277:22260); Wilk *et al.*, (*Mol. Biol. Rep.*, 1997,24:119); Ruiz de Mena *et al.*, (*Biochem. J.* 1993, 296:93); Arribas *et al.*, (*J. Biol. Chem.*, 1990, 265:13969); US 5,847,076 and JP 2002-029996.

30 So far, the known proteasome modulators (inhibitors or activators) present a peptide-like structure and/or have a high molecular weight. These features usually lead to a

weak bioavailability because they may result in a high degradation rate and/or a low capacity to cross the biological membrane.

Besides, the proteasome modulators that covalently interact with proteasome active sites are typically associated with numerous unwanted side effects. Their reactive group is inherently associated with probable lack of specificity, excessive reactivity, and instability.

Therefore, there is a need to have novel proteasome activity modulators, and in particular proteasome activity inhibitors, that are selective of the proteasome with respect to the other intracellular proteases.

There is a need for novel proteasome activity modulators, and in particular proteasome activity inhibitors, having a non-peptide like structure.

There is also a need for novel proteasome activity modulators, and in particular proteasome activity inhibitors, having a low molecular weight.

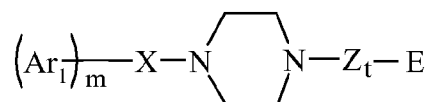
There is also a need for novel proteasome activity modulators, and in particular proteasome activity inhibitors, having a high bioavailability.

There is also a need for novel proteasome modulators, and in particular proteasome activity inhibitors, that non-covalently interact with the active sites of the proteasome.

There is also a need for novel proteasome activity modulators, and in particular proteasome activity inhibitors, having reduced or no unwanted side effects.

The present invention has for object to meet those needs.

According to one of its aspects, the instant invention relates to the use of at least one piperazine derivative of formula (I):



25

wherein

$m = 0$  or  $1$ ,

$\text{Ar}_1$  representing a  $\text{C}_6$ - $\text{C}_{10}$  aryl group, substituted with at least one R group, said R group being chosen among:

30

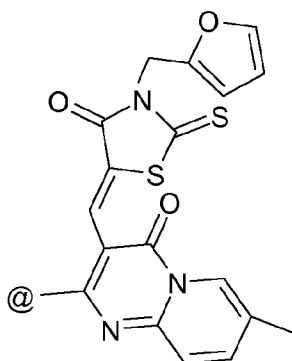
- H, or

- an halogen group, or

- a NO<sub>2</sub> group, or
  - an hydroxyl group, or
  - a linear, branched or cyclic, saturated or unsaturated, C<sub>1</sub>-C<sub>5</sub> alkyl group optionally substituted with a C<sub>6</sub>-C<sub>10</sub> aryl group, or
  - 5        - a linear, branched or cyclic, saturated or unsaturated, C<sub>1</sub>-C<sub>5</sub> aminoalkyl or amidoalkyl group, or
  - a linear, branched or cyclic, saturated or unsaturated, C<sub>1</sub>-C<sub>5</sub> alkoxy group, or
  - a carbonyloxyalkyl group with said alkyl group being a linear, branched, saturated or unsaturated C<sub>1</sub>-C<sub>5</sub> alkyl group,
  - 10       -  $^{*}-(A)_p-(CH_2)_n-B$   
           with  $^{*}$ - representing a covalent bond with Ar<sub>1</sub>, A representing an heteroatom chosen among N, O or S or a carbonyl group, p = 0 or 1, n representing an integer ranging from 0 to 4, and B being chosen from Het<sub>1</sub> or Ar<sub>3</sub>:
  - 15       - Het<sub>1</sub> representing a, saturated or unsaturated, 5-6 membered ring comprising at least one heteroatom, optionally substituted with a C<sub>6</sub>-C<sub>10</sub> aryl group, said aryl group being optionally substituted with one or more NO<sub>2</sub> group(s),
  - Ar<sub>3</sub> representing a C<sub>6</sub>-C<sub>10</sub> aryl group optionally substituted with
  - 20       one or more linear, branched or cyclic, saturated or unsaturated C<sub>1</sub>-C<sub>5</sub> alkoxy group,
- X represents:
- when m = 1,
  - a covalent bond, or
  - 25       -  $^{*}-OCH_2C(O)-\square$  with  $^{*}$ - representing a covalent bond with Ar<sub>1</sub> and  $-\square$  representing a covalent bond with the piperazine-derived radical, or
  - when m = 0,
  - a linear, branched or cyclic, saturated or unsaturated, C<sub>1</sub>-C<sub>5</sub> alkyl group, or
  - C(O)-Het<sub>2</sub>, with Het<sub>2</sub> being as the above-defined Het<sub>1</sub> group,
  - 30       t = 0 or 1,
  - Z representing one group chosen among C(S), (CH<sub>2</sub>)<sub>b</sub> with b = 1 or 2, CH=CH, or S(O)<sub>2</sub>,

E representing:

when  $t = 0$ ,



with @- representing a covalent bond with the piperazine-derived radical,

5 or

when  $t = 1$

@-(R<sup>3</sup>)<sub>q</sub>-(Ar<sub>2</sub>)<sub>r</sub>,

with

@- representing a covalent bond with Z, q and r representing,  
10 independently of each other, 0 or 1,

when  $r = 1$ , R<sup>3</sup> representing a linear or branched, saturated or unsaturated  
C<sub>1</sub>-C<sub>5</sub> alkylene group optionally incorporating at least one heteroatom chosen among N, O  
or S, or being an heteroatom chosen among N, O or S, or when r represents 0, R<sub>3</sub> being a  
linear, branched or cyclic, saturated or unsaturated, C<sub>1</sub>-C<sub>5</sub> alkyl group, optionally  
15 substituted with an hydroxyl, an amino or a thiol group,

Ar<sub>2</sub> representing

when  $m = 0$ , a 5-6 membered heteroaryl group, or

when  $m = 1$ , a C<sub>6</sub> aryl or a 5-6 membered heteroaryl group,

said aryl or heteroaryl group being substituted with at least one R group,

20 said R group being as above-defined,

or a pharmaceutically acceptable salt thereof

as proteasome activity modulator for the preparation of a pharmaceutical composition  
intended to prevent and/or treat a disease condition mediated by the proteasome activity.

The inventors have surprisingly identified piperazine derivatives as novel proteasome activity modulators within a compound collection known and commercially available at Chembridge Corporation ([www.chembridge.com](http://www.chembridge.com)).

5 The compounds of the invention may also be prepared according to methods well-known by the skilled artisan.

Within the meaning of the invention, “proteasome activity modulator” or “proteasome modulator” are used interchangeably and are intended to mean a compound able to bind with at least one active site of the proteasome, i.e. a chymotrypsin-like active site, a trypsin-like active site or a post-acid (PA) active site or with a site distant from said  
10 active sites, and to, directly or allosterically, reduce or even suppress, or increase the enzymatic activity rate of at least one active site as compared with said enzymatic activity rate without said proteasome modulator.

A proteasome modulator of the invention may exert a dual or a multiple effect, that is it may exert an effect on more than one active site.

15 For example, a proteasome modulator may simultaneously exert a reduction, or a suppression, of the enzymatic activity rate of a first active site and an increase or a decrease of the enzymatic activity rate of a second active site. The enzymatic activity rate of a third active site may be reduced or suppressed, or increased or left unchanged.

A proteasome modulator may be a “proteasome activity inhibitor” or  
20 “proteasome inhibitor”.

Within the meaning of the invention, a “proteasome activity inhibitor” or “proteasome inhibitor” is intended to mean a proteasome modulator that reduces or suppresses the enzymatic activity rate of at least one active site of the proteasome, as compared with said enzymatic activity rate determined without said proteasome inhibitor.

25 A proteasome modulator may be a “proteasome activity activator” or “proteasome activator”.

Within the meaning of the invention, a “proteasome activity activator” or “proteasome activator” is intended to mean a proteasome modulator that increases the enzymatic activity rate of at least one active site of the proteasome, as compared with said  
30 enzymatic activity rate determined without said proteasome activator.

According to one embodiment, a proteasome modulator may exert only an inhibitory effect.

According to one embodiment, a proteasome modulator may exert only an activator effect.

According to one embodiment, a proteasome modulator may exert a dual or a multiple effect.

5           According to one embodiment, a proteasome modulator may exert an effect on one, two, or three active sites.

A proteasome modulator exerting an effect on no more than two, and in particular on no more than one active site may advantageously allow to reduce the risk of occurrence of toxic or unwanted side effects.

10           According to one embodiment, a proteasome inhibitor of the invention may inhibit no more than two active sites, and in particular no more than one active site.

According to one embodiment, a proteasome inhibitor may advantageously exert an inhibiting effect on the chymotrypsin-like and/or trypsin-like effect, and in particular on the chymotrypsin-like active site.

15           Within the invention, the term “inhibitor” or “activator” may be attributed to a compound of the invention with respect to an enzyme activity. However, it does not preclude that said compound may also exert an inhibitor and/or activator effect(s) on the other(s) enzyme activity(ies) of the proteasome.

20           Within the meaning of the invention, “pharmaceutical composition” is intended to mean any substance or composition intended to be administered to an individual, human or animal, to prevent, reduce, relieve and/or cure a disease condition or a sign associated with said disease condition and/or to make a diagnostic of a disease condition.

Within the meaning of the invention, the term “prevent” or “prevention” with respect to an event is intended to mean the decrease of a risk of occurrence of said event.

25           According to one embodiment, a disease condition considered in the invention may be chosen among cancers, immunological diseases, auto-immune diseases, allograft rejections, viral diseases, such as mumps, measles, Rous sarcoma or AIDS, parasitic diseases, such as malaria or trypanosome, bacterial infections, such as tuberculosis, inflammatory diseases, such as polyarthritis or liver inflammation, cardiac diseases and  
30           ischemic strokes, such as myocardial, cerebral or pulmonary ischemic injuries, muscular dystrophies, muscle wasting, traumatismes, burns, disease conditions associated with aging, such as neurodegenerative diseases.



According to another aspect, the invention is directed to a use of at least one piperazine derivative in accordance with the invention as active agent in a cosmetic composition for the prevention and/or the treatment of skin aging.

According to another of its aspect, the invention is directed to a kit-of-parts comprising (i) at least one piperazine derivative according to the invention and (ii) at least one agent useful for the prevention and/or the treatment of a cancer condition, said agent being different of said piperazine derivative (i).

According to another of its aspect, the invention is directed to a method for preventing and/or treating a disease condition mediated by proteasome activity comprising at least a step of administering to an individual in need thereof at least one effective amount of at least one piperazine derivative according to the invention.

According to another aspect, the invention relates to a piperazine derivative according to the invention for use as a medicament.

According to one advantage, the novel proteasome modulators of the invention have an improved bioavailability.

According to another advantages, the novel proteasome modulators of the invention have an improved cellular toxicity towards tumoral cells.

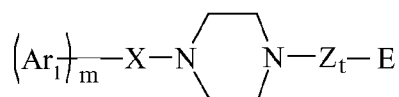
According to another advantages, the novel proteasome modulators of the invention have a low or even have no cellular toxicity on normal healthy cells.

According to another advantage, the novel proteasome modulators of the invention have reduced or no unwanted side-effects.

According to another advantage, the proteasome modulators of the invention are non peptidic molecules without reactive group susceptible to lead to a lack of specificity, excessive reactivity and instability.

### **PROTEASOME MODULATORS**

In one embodiment, a piperazine derivative of the invention may be of formula (I):



wherein  
m = 0 or 1,

Ar<sub>1</sub> representing a C<sub>6</sub>-C<sub>10</sub> aryl, substituted with at least one R group, said R group being chosen among:

- H, or
- an halogen group, or
- 5        - a NO<sub>2</sub> group, or
- an hydroxyl group, or
- a linear, branched or cyclic, saturated or unsaturated, C<sub>1</sub>-C<sub>5</sub> alkyl group optionally substituted with a C<sub>6</sub>-C<sub>10</sub> aryl group, or
- a linear, branched or cyclic, saturated or unsaturated, C<sub>1</sub>-C<sub>5</sub> aminoalkyl or
- 10        amidoalkyl group, or
- a linear, branched or cyclic, saturated or unsaturated, C<sub>1</sub>-C<sub>5</sub> alkoxy group, or
- a carbonyloxyalkyl group with said alkyl group being a linear, branched, saturated or unsaturated C<sub>1</sub>-C<sub>5</sub> alkyl group,

15        -  $^{*}-(A)_p-(CH_2)_n-B$   
               with  $^{*}$ - representing a covalent bond with Ar<sub>1</sub>, A representing an heteroatom chosen among N, O or S or a carbonyl group, p = 0 or 1, n representing an integer ranging from 0 to 4, and B being chosen from Het<sub>1</sub> or Ar<sub>3</sub>:

- Het<sub>1</sub> representing a, saturated or unsaturated, 5-6 membered ring
- 20        comprising at least one heteroatom, optionally substituted with a C<sub>6</sub>-C<sub>10</sub> aryl group, said aryl group being optionally substituted with one or more NO<sub>2</sub> group(s), or
- Ar<sub>3</sub> representing a C<sub>6</sub>-C<sub>10</sub> aryl group optionally substituted with one or more linear, branched or cyclic, saturated or unsaturated C<sub>1</sub>-
- 25        C<sub>5</sub> alkoxy group,

X represents:

when m = 1,

- a covalent bond, or
- $^{*}-OCH_2C(O)-\square$  with  $^{*}$ - representing a covalent bond with Ar<sub>1</sub> and  $-\square$
- 30        representing a covalent bond with the piperazine-derived radical, or

when m = 0,

- a linear, branched or cyclic, saturated or unsaturated, C<sub>1</sub>-C<sub>5</sub> alkyl group,

or

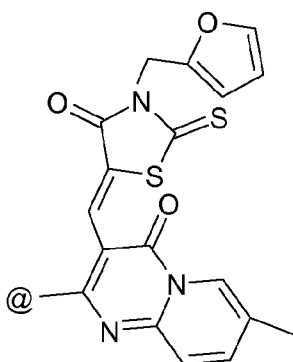
- -C(O)-Het<sub>2</sub>, with Het<sub>2</sub> being as the above-defined Het<sub>1</sub> group.

t = 0 or 1,

5 Z representing one chosen among C(S), (CH<sub>2</sub>)<sub>b</sub> with b = 1 or 2, CH=CH, or S(O)<sub>2</sub>,

E representing:

when t = 0,



10 with @- representing a covalent bond with the piperazine-derived radical, or  
when t = 1

@-(R<sup>3</sup>)<sub>q</sub>-(Ar<sub>2</sub>)<sub>r</sub>,

with

@- representing a covalent bond with Z, q and r representing,

15 independently of each other, 0 or 1,

when r = 1, R<sup>3</sup> representing a linear or branched, saturated or unsaturated

C<sub>1</sub>-C<sub>5</sub> alkylene group optionally incorporating at least one heteroatom chosen among N, O

or S, or being an heteroatom chosen among N, O or S, or when r represents 0, R<sup>3</sup> being a

linear, branched or cyclic, saturated or unsaturated, C<sub>1</sub>-C<sub>5</sub> alkyl group, optionally

20 substituted with an hydroxyl, an amino or a thiol group,

Ar<sub>2</sub> representing

when m = 0, a 5-6 membered heteroaryl group, or

when m = 1, a C<sub>6</sub> aryl or a 5-6 membered heteroaryl group,

said aryl or heteroaryl group being substituted with at least one R group,

25 said R group being as above-defined,

or a pharmaceutically acceptable salt thereof

as proteasome activity modulator for the preparation of a pharmaceutical composition intended to prevent and/or treat a disease condition mediated by the proteasome activity.

5           The terms “pharmaceutically acceptable salt” are intended to mean a compound which may be obtained by reaction of a compound of general formula (I) with an acid.

As examples of acid suitable for the invention, one may mention chlorhydric acid, bromhydric acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulfonic acid, 10 methane sulfonic acid, acetic acid, citric acid, maleic acid, salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzene sulfonic acid, tartaric acid and the like, and their mixtures, in solvent such as ethylacetate, ether, alcohol solvent, acetone, THF, dioxane, and the like and their mixtures.

The invention also relates to isoform of compounds of formula (I).

15           Within the meaning of the invention, the term “isoform” is intended to mean tautomers, stereoisomers, polymorphous forms or pharmaceutically acceptable solvates.

The term “tautomer” is intended to mean isomers, the structure of which differs by the position of one atom, typically one hydrogen atom, and one or more multiple bonds and which are able to easily and reversibly transform into each other.

20           The term “stereoisomer” is intended to mean isomers from a molecule which are identical in constitution but which differ only by one or more different arrangements of their atoms in space.

The terms “polymorphous form” are intended to mean compounds obtained by crystallization of a compound of general formula (I) in different conditions, as for example 25 the use of different sequences, usually used for crystallization. Crystallization at different temperature implies, for example, various mode of cooling, such as very fast to very low cooling, or warming or melting steps of compounds followed by fast or gradual cooling.

The presence of polymorphous forms may be identified by NMR spectroscopy, IR-spectroscopy (infrared), differential scanning calorimetry (DSC), X-ray diffraction or 30 other similar techniques known in the art.

Within the meaning of the invention, the term “unsaturated” with respect to a group from the formula (I) is intended to mean that this group may comprise one or more multiple bond(s), such as double or triple bond(s).

When a given group from formula (I) comprises more than one unsaturated bonds, for example at least two double bonds, those unsaturated bonds may or may not be conjugated between them in said group and/or conjugated with unsaturated bond(s) of the other moieties of the formula (I).

In particular, with respect to alkyl group, unsaturated is intended to mean alkenyl or alkynyl group.

According to one embodiment, Ar<sub>1</sub> and/or Ar<sub>2</sub> may represent, independently of each other, an aryl group chosen among a phenyl group, a naphthyl group, or an heteroaryl comprising at least one heteroatom chosen among N, O or S.

As example of heteroaryl that may convene to the invention, one may mention a pyridine group, a quinoline or isoquinoline group, an aza- or diazanaphthalene group, or a thiophen group.

According to one embodiment, Ar<sub>1</sub> may be chosen among a phenyl group or a naphthyl group, and in particular may be a phenylgroup .

According to one embodiment, Ar<sub>2</sub> may be chosen among a phenyl group, a pyridine group or a thiophen group, and in particular may be a phenyl group.

More particularly, Ar<sub>1</sub> and Ar<sub>2</sub> may represent a phenyl group.

According to another embodiment, Ar<sub>1</sub> may be substituted with at least two R<sup>1</sup> groups, identical or different, said R<sup>1</sup> groups being as the R group above-defined.

More particularly, R<sup>1</sup> may be chosen among:

- H, or
- an halogen group, in particular Cl or Br, or
- NO<sub>2</sub>, or
- a linear, branched or cyclic, saturated or unsaturated C<sub>2</sub>-C<sub>4</sub> alkyl group, in particular a methyl, an ethyl, a propyl, an iso-propyl, a n-butyl, an iso-, a sec- or a tert-butyl group, and more particularly a methyl, an ethyl or an iso-propyl group, or
- a linear, branched or cyclic, saturated or unsaturated C<sub>2</sub>-C<sub>4</sub> aminoalkyl group, in particular an aminomethyl, an aminoethyl, an aminopropyl, an iso-aminopropyl, a n-aminobutyl, an iso-, a sec- or a tert-aminobutyl group, or

- a linear, branched or cyclic, saturated or unsaturated C<sub>2</sub>-C<sub>4</sub> alkoxy group, in particular a methoxy, an ethoxy, a propoxy, an iso-propoxy, a n-butoxy, an iso-, a sec- or a tert-butoxy group,

-  $^{*}-(A)_p-(CH_2)_n-B$ , with  $^{*}$ - being as above-defined, A being N, S, or C(O), n ranging from 0 to 3, and in particular from 1 to 2, and B being Het<sub>1</sub> or Ar<sub>3</sub>:

- Het<sub>1</sub> representing a saturated or unsaturated heterocyclic group comprising at least one heteroatom chosen among oxygen, sulfur and nitrogen, optionally substituted with one or more NO<sub>2</sub> group(s), or
- Ar<sub>3</sub> representing a phenyl or a naphthyl group, in particular a phenyl group, optionally substituted with an alkoxy group as above-defined.

According to one embodiment, Het<sub>1</sub> may be an heterocyclic group chosen among a tetrahydrofuran, a furan, a pyran, an oxazine, an oxazole, an oxadiazole, a thiazole, an isothiazole, a pyrrole, a pyrazole, an imidazole, a piperidine, a pyridine, a pyrazine, a pyrimidine, a pyridazine, or a piperazine derived radical.

According to one embodiment, Ar<sub>3</sub> may be substituted with one or more, in particular at least two, linear, branched or cyclic, saturated or unsaturated, C<sub>2</sub>-C<sub>4</sub> alkoxy group(s), in particular one or more methoxy, ethoxy, propoxy or iso-propoxy group(s).

According to one embodiment, when R<sup>1</sup> group(s) represent(s) an electronegative functional group and Ar<sub>1</sub> is a phenyl group, said R<sup>1</sup> group(s) may be in position *meta* and/or *para* of Ar<sub>1</sub> with respect to the X moiety.

According to another embodiment, when said R<sup>1</sup> group(s) represent(s) an electropositive group and Ar<sub>1</sub> is a phenyl group, said R<sup>1</sup> group(s) may be in position *ortho* and/or *para* of Ar<sub>1</sub> with respect to the X moiety.

According to one embodiment, when said R<sup>1</sup> group represents  $^{*}-(A)_p-(CH_2)_n-B$  and Ar<sub>1</sub> is a phenyl group, said R<sup>1</sup> may be in position *meta* of Ar<sub>1</sub> with respect to the X moiety.

According to one embodiment, when said R<sup>1</sup> group(s) represent(s) NO<sub>2</sub> and Ar<sub>1</sub> is a phenyl group, said R<sup>1</sup> may be in position *ortho* and/or *para* of Ar<sub>1</sub> with respect to the X moiety, and in particular is in position *para*.

According to one embodiment, when said R<sup>1</sup> group represents an alkyl group, and in particular a methyl group, and Ar<sub>1</sub> is a phenyl group, said R<sup>1</sup> may be in position *ortho* of Ar<sub>1</sub> with respect to the X moiety.

According to one embodiment, when said  $R^1$  group represents an halogen, and in particular Cl, and  $Ar_1$  is a phenyl group, said  $R^1$  may be in position *meta* and/or *para* of  $Ar_1$  with respect to the X moiety.

According to one embodiment, when  $m = 0$ , X may be a linear, branched or cyclic, saturated or unsaturated,  $C_2$ - $C_4$  alkyl group, in particular a methyl, an ethyl, a propyl, an iso-propyl group, or a  $-C(O)-Het_2$  group, with  $Het_2$  being chosen among a tetrahydrofuran, a furan, a pyran, an oxazine, an oxazole, an oxadiazole, a thiazole, an isothiazole, a pyrrole, a pyrazole, an imidazole, a piperidine, a pyridine, a pyrazine, a pyrimidine, a pyridazine, or a piperazine group, and in particular is a tetrahydrofuran derived radical.

According to one embodiment,  $Ar_2$  may be substituted with at least two  $R^2$  groups, identical or different, said  $R^2$  groups being as the R group above-defined.

More particularly,  $R^2$  may be chosen among:

- H, or
- an halogen group, in particular Cl or Br, or
- a linear, branched or cyclic, saturated or unsaturated,  $C_2$ - $C_4$  alkyl group, in particular a methyl, an ethyl, a propyl, an iso-propyl, a n-butyl, an iso-, a sec- or a tert-butyl group, or
- a linear, branched or cyclic, saturated or unsaturated,  $C_2$ - $C_4$  alkoxy group, in particular a methoxy, an ethoxy, a propoxy or an iso-propoxy group, a n-butoxy, an iso-, a sec- or a tert-butoxy group, or
- a linear, branched or cyclic, saturated or unsaturated,  $C_2$ - $C_4$  amidoalkyl group, in particular an amidomethyl, an amidoethyl, an amidopropyl or an amido-iso-propyl group, an amido-n-butyl, an-amido-iso-, an amido-sec- or an amido-tert-butyl group, or
- a carbonyloxyalkyl group with said alkyl group being a linear, branched, saturated or unsaturated  $C_2$ - $C_4$  alkyl group, in particular being a methyl, an ethyl or a propyl group.

According to one embodiment, when  $R^2$  group represent an electronegative functional group and  $Ar_2$  is a phenyl group, said  $R^2$  group may be in position *para* of  $Ar_2$  with respect to the  $-Z_t-(R^3)_q$  moiety, and/or when said  $R^2$  group(s) represent(s) an

electropositive group and Ar<sub>2</sub> is a phenyl group, said R<sup>2</sup> group(s) may be in position *meta* and/or *para* of Ar<sub>2</sub> with respect to the -Z<sub>t</sub>-(R<sup>3</sup>)<sub>q</sub> moiety.

When said R<sup>2</sup> group represents an alkyl group, and in particular a methyl or an iso-propyl or an iso-butyl group, and Ar<sub>2</sub> is a phenyl group, said R<sup>2</sup> may be in position  
5 *para* of Ar<sub>2</sub> with respect to the -Z<sub>t</sub>-(R<sup>3</sup>)<sub>q</sub> moiety.

According to one embodiment, when said R<sup>2</sup> group represents an halogen group, and in particular Cl, and Ar<sub>2</sub> is a phenyl group, said R<sup>2</sup> may be in position *para* of Ar<sub>2</sub> with respect to the -Z<sub>t</sub>-(R<sup>3</sup>)<sub>q</sub> moiety.

According to one embodiment, when said R<sup>2</sup> group(s) represent(s) (an) alkoxy  
10 group(s), and in particular a methoxy and/or an ethoxy group, and Ar<sub>2</sub> is a phenyl group, said R<sup>2</sup> may be in position *meta* and/or *para* of Ar<sub>2</sub> with respect to the -Z<sub>t</sub>-(R<sup>3</sup>)<sub>q</sub> moiety.

According to one embodiment, when said R<sup>2</sup> group represents an amidoalkyl group, and in particular an amidomethyl group, and Ar<sub>2</sub> is a phenyl group, said R<sup>2</sup> may be in position *para* of Ar<sub>2</sub> with respect to the -Z<sub>t</sub>-(R<sup>3</sup>)<sub>q</sub> moiety.

According to one embodiment, R<sup>3</sup> may represent a linear, branched or cyclic,  
15 saturated or unsaturated, C<sub>2</sub>-C<sub>4</sub> alkylene group, and in particular a methylene, an ethylene, a propylene, an isopropylene, or an ethylene group, optionally incorporating at least one heteroatom chosen among O, N or S.

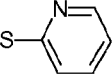
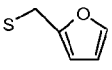
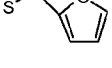
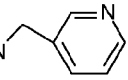
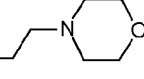
According to one embodiment, R<sup>3</sup> may represent one heteroatom chosen  
20 among N, O, or S, and in particular may be N.

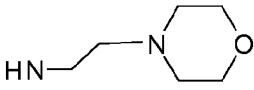
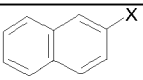
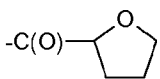
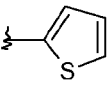
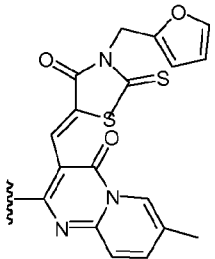
According to one embodiment, when r represents 0, R<sup>3</sup> may be an alkyl group as above-defined substituted with one or more, and in particular with at least two, hydroxyl, amino or thiol group(s).

According to one embodiment, when r represents 0, R<sup>3</sup> may represent an  
25 hydroxyalkyl ranging from C<sub>2</sub> to C<sub>4</sub>, and in particular is an hydroxy methyl, an hydroxy-1-ethyl, an hydroxyl-2-ethyl or an hydroxyl-3 propyl group.

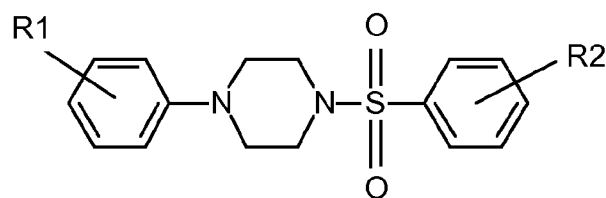
According to one embodiment, a piperazine derivative of the invention may be of formula (I) as previously described wherein m, Ar<sub>1</sub>, R<sup>1</sup>, X, Z, t, E, R<sup>3</sup>, Ar<sub>2</sub>, R<sup>2</sup>, q and r are as defined in the following table:



| Cpd       | Ar <sub>1</sub>                                                                     | R <sup>1</sup>                                                                                                                 | Z                 | E represents $-(R^3)_q-(Ar_2)_r$ |                                                                                       |                                                                  |
|-----------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------------------------|---------------------------------------------------------------------------------------|------------------------------------------------------------------|
|           |                                                                                     |                                                                                                                                |                   | R <sup>3</sup>                   | Ar <sub>2</sub>                                                                       |                                                                  |
|           | <b>m = 1, X :<br/>covalent bond</b>                                                 |                                                                                                                                | <b>t = 1</b>      | <b>q = 0</b>                     | <b>r = 1</b>                                                                          | <b>R<sup>2</sup></b>                                             |
| <b>1</b>  |    | <i>p</i> -NO <sub>2</sub>                                                                                                      | S(O) <sub>2</sub> |                                  |    | <i>p</i> -CH <sub>2</sub> -<br>CH(CH <sub>3</sub> ) <sub>2</sub> |
| <b>2</b>  |    | <i>o</i> -CH <sub>3</sub> ,<br><i>m</i> -Cl                                                                                    | S(O) <sub>2</sub> |                                  |    | <i>p</i> -C(CH <sub>3</sub> ) <sub>3</sub>                       |
| <b>3</b>  |    | <i>o</i> -NO <sub>2</sub> ,<br><i>p</i> -Cl                                                                                    | S(O) <sub>2</sub> |                                  |    | <i>p</i> -C(CH <sub>3</sub> ) <sub>3</sub>                       |
| <b>4</b>  |    | <i>p</i> NO <sub>2</sub> ,<br><br><i>m</i>    | S(O) <sub>2</sub> |                                  |    | <i>p</i> -Cl                                                     |
| <b>5</b>  |   | <i>p</i> -NO <sub>2</sub> ,<br><br><i>m</i> | S(O) <sub>2</sub> |                                  |  | <i>p</i> -CH <sub>3</sub>                                        |
| <b>6</b>  |  | <i>p</i> -NO <sub>2</sub> ,<br><br><i>m</i> | S(O) <sub>2</sub> |                                  |  | <i>p</i> -Cl                                                     |
| <b>7</b>  |  | <i>p</i> -NO <sub>2</sub> ,<br><br><i>m</i> | S(O) <sub>2</sub> |                                  |  | <i>p</i> -C(CH <sub>3</sub> ) <sub>3</sub>                       |
| <b>8</b>  |  | <i>p</i> -NO <sub>2</sub> ,<br><br><i>m</i> | S(O) <sub>2</sub> |                                  |  | <i>p</i> -NH-CO-<br>CH <sub>3</sub>                              |
| <b>9</b>  |  | <i>p</i> -NO <sub>2</sub> , <i>m</i> -NH-CH <sub>2</sub> -<br>CH(CH <sub>3</sub> ) <sub>3</sub>                                | S(O) <sub>2</sub> |                                  |  | <i>m</i> -O-CH <sub>3</sub> , <i>p</i> -<br>O-CH <sub>3</sub>    |
|           |                                                                                     |                                                                                                                                |                   | <b>q = 1</b>                     |                                                                                       |                                                                  |
| <b>10</b> |  | <i>p</i> -OCH <sub>3</sub>                                                                                                     | C(S)              | NH                               |  | <i>p</i> -NO <sub>2</sub>                                        |
| <b>11</b> |  | <i>p</i> -NO <sub>2</sub> ,                                                                                                    | S(O) <sub>2</sub> | CH                               |                                                                                       | H                                                                |

|           |                                                                                                                                                            |                                                                                   |                 |              |                                                                                      |   |
|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------|--------------|--------------------------------------------------------------------------------------|---|
|           |                                                                                                                                                            |  |                 |              |   |   |
|           | <b>m = 1, and X represents <math>^*\text{-OCH}_2\text{CO-}</math></b><br> |                                                                                   |                 | <b>q = 0</b> | <b>r = 1</b>                                                                         |   |
| <b>12</b> |                                                                           | H                                                                                 | $\text{S(O)}_2$ |              |   | H |
|           | <b>m = 0</b> <b>X represents <math>\text{-C(O)-}</math></b><br><b>Het<sub>2</sub></b>                                                                      |                                                                                   |                 | <b>q = 1</b> |                                                                                      |   |
| <b>13</b> |                                                                           |                                                                                   | $\text{C(S)}$   | NH           |   | H |
|           | <b>m = 0</b> <b>X represents a <math>\text{C}_1\text{-C}_5</math> alkyl</b><br><b>group</b>                                                                |                                                                                   | <b>t = 0</b>    |              | <b>E represents</b>                                                                  |   |
| <b>14</b> | $\text{-CH}_2\text{CH}_3$                                                                                                                                  |                                                                                   |                 |              |  |   |

According to one embodiment, a piperazine derivative of the invention may be of formula



(IIA)

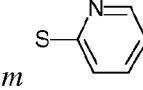
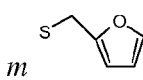
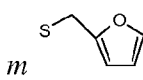
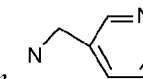
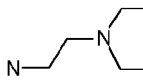
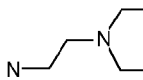
5

wherein

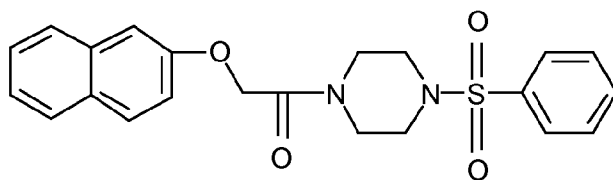
$\text{R}^1$  and  $\text{R}^2$  are as above-defined.

According to one embodiment, a piperazine derivative of the invention may be of formula (IIA) as above-defined, wherein  $\text{R}^1$  and  $\text{R}^2$  are as defined in the following table:

10

| Compound | R <sup>1</sup>                                                                                                                 | R <sup>2</sup>                                               |
|----------|--------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| 1        | <i>p</i> -NO <sub>2</sub>                                                                                                      | <i>p</i> -CH <sub>2</sub> -CH(CH <sub>2</sub> ) <sub>2</sub> |
| 2        | <i>o</i> -CH <sub>3</sub> ,<br><i>m</i> -Cl                                                                                    | <i>p</i> -C(CH <sub>3</sub> ) <sub>3</sub>                   |
| 3        | <i>o</i> -NO <sub>2</sub> ,<br><i>p</i> -Cl                                                                                    | <i>p</i> -C(CH <sub>3</sub> ) <sub>3</sub>                   |
| 4        | <i>p</i> NO <sub>2</sub> ,<br><br><i>m</i>    | <i>p</i> -Cl                                                 |
| 5        | <i>p</i> -NO <sub>2</sub> ,<br><br><i>m</i>  | <i>p</i> -CH <sub>3</sub>                                    |
| 6        | <i>p</i> -NO <sub>2</sub> ,<br><br><i>m</i> | <i>p</i> -Cl                                                 |
| 7        | <i>p</i> -NO <sub>2</sub> ,<br><br><i>m</i> | <i>p</i> -C(CH <sub>3</sub> ) <sub>3</sub>                   |
| 8        | <i>p</i> -NO <sub>2</sub> ,<br><br><i>m</i> | <i>p</i> -NH-CO-CH <sub>3</sub>                              |
| 9        | <i>p</i> -NO <sub>2</sub> ,<br><i>m</i> -NH-CH <sub>2</sub> -<br>CH(CH <sub>3</sub> ) <sub>3</sub>                             | <i>m</i> -O-CH <sub>3</sub><br><i>p</i> -O-CH <sub>3</sub>   |
| 11       | <i>p</i> -NO <sub>2</sub> ,<br><br><i>m</i> | H                                                            |

or of formula (II B)



12 (II B)

According to one embodiment, a piperazine derivative in accordance with the invention that may be particularly useful for the invention may be compound 7 or 12.

As exposed in the examples section, the piperazine derivatives of the invention present an  $IC_{50}$  (concentration of compound able to half inhibit an enzymatic activity rate as compared to said enzymatic activity rate without said compound) on the chymotrypsin-like activity lower or equal to 100  $\mu M$ , in particular lower or equal to 80  $\mu M$ , in particular lower or equal to 70  $\mu M$ , in particular lower or equal to 50  $\mu M$ , in particular lower or equal to 20  $\mu M$ , in particular lower or equal to 10  $\mu M$ , in particular lower or equal to 5  $\mu M$ , in particular lower or equal to 2  $\mu M$ .

Furthermore, the piperazine derivatives of the invention present an  $IC_{50}$  on the post-acide (PA) activity lower or equal to 100  $\mu M$ , in particular lower or equal to 50  $\mu M$ , in particular lower or equal to 25  $\mu M$ , in particular lower or equal to 10  $\mu M$ , in particular lower or equal to 5  $\mu M$ , in particular lower or equal to 2  $\mu M$ , in particular lower or equal to 1  $\mu M$ , in particular lower or equal to 0.6  $\mu M$ , in particular lower or equal to 0.2  $\mu M$  and more particularly lower or equal to 0.1  $\mu M$ .

Additionally, the piperazine derivatives of the invention exhibit an  $EC_{50}$  (concentration of a compound able to induce half the effect of a given pharmacological effect as compared to the maximum effect obtained with said compound) with regard to their toxicity on tumoral cells, lower or equal to 10  $\mu M$ , in particular lower or equal to 8  $\mu M$ , in particular lower or equal to 5  $\mu M$ , in particular lower or equal to 2  $\mu M$  and more particularly lower or equal to 1  $\mu M$ .

The piperazine derivatives of the invention present a low molecular weight, in particular lower than 600 g/mol, in particular lower than 550 g/mol, and more particularly lower than 500 g/mol, and have a non-peptide-like structure.

**PHARMACEUTICAL OR COSMETIC COMPOSITIONS**

The term “pharmaceutical” or “medicament”, used herein interchangeably, refers to an agent or mixture of agents that is primarily intended to treat and/or ameliorate and/or prevent a disease or a disorder or to diagnostic a disease or a disorder.

5           The term “pharmaceutically acceptable” means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable and includes what is acceptable for veterinary as well as human pharmaceutical use.

10           Within the meaning of the invention, the term “cosmetic composition” is intended to have the meaning as exposed in the European Directive 76/768/CEE.

          More particularly, a “cosmetic composition” may be any substance or preparation intended to be placed in contact with the various external parts of the human body (skin, hair, nail, lips, ...), or with the teeth or mucous membranes of the oral cavity for, exclusively or mainly, cleaning them, perfuming them, changing their appearance,  
15           and/or correcting body odors, and/or protecting them or keeping them in good condition.

          According to one embodiment, a piperazine derivative of the invention may be used as a cosmetic agent.

          An “effective amount” means an amount sufficient to induce a positive modification in the condition to be regulated or treated, but low enough to avoid serious  
20           side effects. An effective amount may vary with the cosmetic or pharmaceutical effect to obtain or with the particular condition being treated, the age and physical condition of the end user, the severity of the condition being treated/prevented, the duration of the treatment, the nature of other treatments, the specific compound or product/composition employed, the route of administration, and like factors.

25           The term “subject” or “individual”, used interchangeably herein, means mammals and non-mammals. Examples of mammals include, but are not limited to: humans; non-human primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, and swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice, and guinea  
30           pigs; and the like. Examples of non-mammals include, but are not limited to, birds, and the like. The term “subject” or “individual” does not denote a particular age or sex.

A piperazine derivative of the present invention may be administered in an effective amount by any of the accepted modes of administration in the art.

In one embodiment, a piperazine derivative may be used in a composition intended to be administered by oral, nasal, sublingual, aural, ophthalmic, topical, rectal,  
5 vaginal, urethral, or parenteral injection route.

The route of administration and the galenic formulation will be adapted by one skilled in the art pursuant to the desired cosmetic or pharmaceutical effect.

In one embodiment, suitable concentration may range from 0.0001 mg/kg/d to 50 mg/kg/d, in particular from 0.001 mg/kg/d to 5 mg/kg/d and more particularly from  
10 0.01 to 0.5 mg/kg/d, depending upon numerous factors such as the age and relative health of the subject, the potency of the formulation used, and the therapeutic or cosmetic indication towards which the administration is directed.

One of ordinary skill in the art of therapeutic formulations or cosmetic formulations will be able, without undue experimentation and in reliance upon personal  
15 knowledge and the disclosure of this application, to ascertain a therapeutically or cosmetically effective amount of a piperazine derivative of the invention for a given indication.

A pharmaceutical composition of the invention may be formulated with any known suitable pharmaceutically acceptable carrier according to the dose, the galenic  
20 form, the route of administration and the likes.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in a medicament of the invention is  
25 contemplated.

A pharmaceutical or a cosmetic composition of the invention may be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, sprays, ointments, gels, creams, sticks, lotions, pastes, soft and hard gelatin capsules, suppositories, sterile injectable solutions, sterile packaged powders  
30 and the likes.

According to one embodiment, a cosmetic composition of the invention may be in particular adapted to be administered by topical route.

A cosmetic composition of the invention may comprise any excipient usually used in the cosmetic art, such as hydrophilic or lipophilic gelifying agent, hydrophilic or lipophilic additives, antioxidants, conservative agents, solvents, perfumes, fillers, UV screens, moisturizers, odor absorbing agents, and coloring agents.

5           According to one embodiment, a pharmaceutical composition of the invention may be intended to be administered separately, sequentially or simultaneously with an agent useful for the prevention and/or the treatment of a disease condition, in particular a cancer condition, said agent being different from the piperazine derivative of the invention.

          According to one embodiment, a pharmaceutical composition of the invention  
10   may be intended to be administered separately, sequentially or simultaneously with a chemotherapeutic agent or a radiotherapeutic regimen.

### **KIT-OF-PARTS**

          The invention is also directed to a novel kit-of-parts that is suitable for use in  
15   the treatment of cancers.

A kit-of-part of the invention may comprise (i) at least one piperazine derivative, as defined above, and (ii) at least one agent useful for the prevention and/or the treatment of a cancer condition, said agent being different of said piperazine derivative.

          According to one embodiment, the kit-of-part of the invention may comprise  
20   (i) at least one piperazine derivative, as defined above, and (ii) at least one agent as above-defined, each of (i) and (ii) being laid out to be administered separately, sequentially or simultaneously.

An agent useful for the prevention and/or the treatment of a cancer condition may be a chemotherapeutic agent or a radiotherapeutic agent.

25           As example of chemotherapeutic agents that may be suitable for the invention, one may mention chemotherapeutic agents chosen from alkylating agents, nitrosoureas, anti-metabolite agents, anti-tumor antibiotics, plant alkaloids, steroid hormones, monoclonal antibodies, and mixtures thereof.

          As example of alkylating agents that may be used in accordance with the  
30   invention, one may mention chlorambucil and cyclophosphamide.

          As example of nitrosoureas that may be used in accordance with the invention, one may mention carmustine and lomustine.

As example of anti-metabolite agents that may be used in accordance with the invention, one may mention fludarabine, 6-mercaptopurine and 5-fluorouracil (5 FU).

As example of anti-tumor antibiotics that may be used in accordance with the invention, one may mention the mitomycin-C, the bleomycin, and the anthracyclines such as the doxorubicine.

As example of plant alkaloids that may be used in accordance with the invention, one may mention vincristine and vinblastine.

As example of steroid hormones that may be used in accordance with the invention, one may mention tamoxiphen, prednisone, dexamethasone.

As example of monoclonal antibodies that may be used in accordance with the invention, one may mention rituximab and alemtuzumab.

According to one embodiment, the additional agent useful for the prevention and/or the treatment of a cancer condition (ii) may be an agent useful for the prevention and/or the treatment of B cell lymphoma, and more particularly for the prevention and/or treatment of multiple myeloma or mantle cells lymphoma.

As example of such suitable agent, one may mention melphalan, vincristine, doxorubicin, cyclophosphamide, fludarabine, thalidomide, prednisone or dexamethasone, cytosine arabinoside, methotrexate or rituximab.

Advantageously, those agents may be used in combination more particularly adapted to a given disease condition such as melphalan and prednisone or thalidomide and dexamethasone, or cyclophosphamide and fludarabine or vincristine and doxorubicin and dexamethasone for multiple myeloma or rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone for mantle cells lymphoma.

As example of radiotherapeutic agent that may be used in accordance with the invention, one may mention an isotope such as for example chosen from  $^{14}\text{C}$ ,  $^3\text{H}$ , or  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{32}\text{P}$ ,  $^{89}\text{Sr}$ ,  $^{90}\text{Y}$ , administered as radio-labeled antibodies

According to one embodiment, a kit-of-parts of the invention may comprise (i) at least one piperazine derivative, as defined above, and (ii) at least one agent useful for the prevention and/or the treatment of a cancer condition, said agent being different of said piperazine derivative and in particular being chosen among histone deacetylase inhibitors.

Histone deacetylase inhibitor (HDAC inhibitors or HDI) are a class of compounds that interfere with the fonction of histone deacetylase.



Among the HDIs that may be used in the invention, one may mention hydroxamic acids, such as trichostatin<sup>1</sup>, cyclic tetrapeptides, such as trapoxin B and the depsipeptides, the benzamides, the electrophilic ketones, and the aliphatic acids compounds such as phenylbutyrate and valproic acid.

- 5           According to another embodiment, a HDI that may be used in accordance with the invention may be, for example, SAHA/vorinostat, belinostat/PXD1001, MS275, LAQ824/LBH589, CI994, or MGCD0103.

### **METHODS OF TREATMENT**

- 10           According to one embodiment, the instant invention relates to a method for preventing and/or treating a disease condition comprising at least a step of administering to an individual in need thereof at least an effective amount of at least one piperazine derivative in accordance with the invention.

- The disease condition may be chosen among cancers, immunological diseases,  
15   auto-immune diseases, allograft rejections, viral diseases, such as mumps, measles, Rous sarcoma or AIDS, parasitic diseases such as malaria or trypanosome, bacterial infections, such as tuberculosis, inflammatory diseases, such as polyarthritis or liver inflammation, cardiac diseases and ischemic strokes, such as myocardial, cerebral or pulmonary ischemic injuries, muscular dystrophies, muscle wasting, traumatismes, burns, disease conditions  
20   associated with aging, such as neurodegenerative diseases.

- According to one embodiment, a disease condition may be chosen among lung and oro-pharynx cancers, colo-rectal cancers, gastro-intestinal tract cancers, breast cancers, prostate cancers, pancreas cancers, leukemias such as Hodgkin's disease, immunoproliferative tumors, in particular B-cells lymphomas or multiple myeloma,  
25   bladder cancers, kidney cancers, ovarian cancers, cervical cancers, brain cancers, head and neck cancers, skin cancers, in particular melanoma or bone cancers.

          According to one embodiment, a disease condition may be a cancer condition, and in particular a B-cells lymphoma.

- According to another embodiment, a disease condition may be chosen among  
30   follicular lymphoma, small non-cleaved cell lymphoma, such as endemic Burkitt's or sporadic Burkitt's or non-Burkitt's lymphoma, marginal zone lymphoma, such as mucosa-associated lymphoid tissue (MALT-MALT-oma) (extranodal), or monocytoid B-cell

lymphoma (nodal) or splenic lymphoma with villous lymphocytes, mantle cell lymphoma, large cell lymphoma, such as diffused large cell, or diffused mixed cell or immune-blastic lymphoma or primary mediastinal B-cell lymphoma or angiocentric lymphoma-pulmonary B-cell, and small lymphocytic lymphoma.

5           According to another embodiment, a disease condition may be a mantle cell lymphoma.

          According to another embodiment, a disease condition may be a multiple myeloma.

          According to one embodiment, a method of the invention may comprise the  
10   step of administering a piperazine derivative in accordance with the invention separately, sequentially or simultaneously with a chemotherapeutic agent or a radiotherapeutic regimen.

          A chemotherapeutic agent may be as above-described.

          A radiotherapeutic regimen may be administered by exposing an individual in  
15   need thereof to a source of ionizing radiation such as X-ray, gamma-ray or beta-ray.

          A source of ionizing radiation that may convene to the invention may be, for example, external source such as radioactive cobalt or a digital linear accelerator producing X-rays or an administrated source under the form of an isotope such as for example from  $^{14}\text{C}$ ,  $^3\text{H}$ , or  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{32}\text{P}$ ,  $^{89}\text{Sr}$ ,  $^{90}\text{Y}$ .

20           For example, the isotopes may be administered as radio-labeled antibodies.

          According to another embodiment, the invention is directed to a use of at least one piperazine derivative in accordance with the invention as active agent in a cosmetic composition for the prevention and/or the treatment of skin aging.

          In one embodiment a piperazine derivative to be used for cosmetic purposes  
25   may be advantageously a proteasome activator.

          The skin aging may be from chronologic origin, and/or may be indicative of a cutaneous condition, resulting, for example, from the photoaging.

          Accordingly, a cosmetic composition of the invention may be intended to prevent and/or to treat a thinning of an epidermis and/or a lost of firmness, elasticity,  
30   density and/or tonicity of an epidermis and/or the formation of wrinkles.

          According to another embodiment, the invention relates to a cosmetic method for preventing and/or treating the skin aging comprising at least the step of administering

to an individual in need thereof at least one effective amount of a piperazine derivative of the invention.

The present invention will be better understood by referring to the following examples which are provided for illustrative purpose only and should not be interpreted as  
5 limiting in any manner the instant invention.

### **FIGURES**

**Figure 1:** Percentage of inhibition of the CT-L active site by increasing concentration of a piperazine derivative compound (7) of the invention at pH 8 and 37°C.

10 **Figure 2:** Cytotoxic effect of a piperazine derivative compound (7) of the invention on HeLa cells treated for 48 hours at 37°C. The cell viability is determined with an XTT assay.

### **EXAMPLES**

#### 15 Example 1

##### **Effects on proteasome activities**

The 14 following compounds are known and commercially available from ChemBridge corporation ([www.chembridge.com](http://www.chembridge.com)). The compounds were dissolved in DMSO to 10 mM stock concentrations and stored at -20°C.

20 Rabbit reticulocyte 20S proteasome was obtained from Boston Biochem, Cambridge, USA. The fluorogenic substrates Suc-LLVY-AMC, Boc-LRR-AMC and Z-LLE-βNA used to measure the proteasome activities CT-L, T-L and PA respectively were purchased from Bachem (France). Other reagents and solvents were purchased from commercial sources. Fluorescence was measured using a BMG Fluostar microplate reader.

25 The 14 compounds were tested for their potential to inhibit the CT-L, T-L and PA activities of the rabbit reticulocyte 20S proteasome. Enzyme activities were determined by monitoring the hydrolysis of the appropriate fluorogenic substrate ( $\lambda_{\text{exc}} = 360$ ,  $\lambda_{\text{em}} = 465$  nm for AMC substrates, and  $\lambda_{\text{exc}} = 340$ ,  $\lambda_{\text{em}} = 405$  nm for the βNA substrate) for 1 h at 37°C.

30 In the *in vitro* screening, each compound was tested in duplicate against the three activities, at 100 μM and 50 μM in the corresponding buffer. The buffer were (pH 8): 50 mM Tris, 150 mM NaCl, 10% (v/v) glycerol, 0.025% (w/v) SDS, and 3% (v/v) DMSO

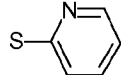
(CT-L and PA activities); 50 mM Tris, 150 mM NaCl, 10% (v/v) glycerol, and 3% (v/v) DMSO (T-L activity). Compounds with inhibitor efficiency superior at 50% at 100  $\mu$ M for any proteasome activity were retested with 0.1-100  $\mu$ M of test compound.

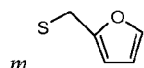
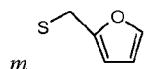
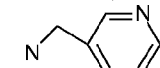
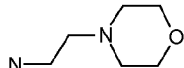
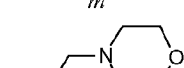
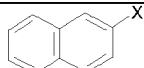
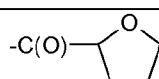
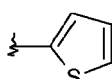
The inhibitory activity of compounds is expressed as  $IC_{50}$ , which corresponds to the concentration of proteasome inhibitor leading to a loss of activity of 50%. The values of  $IC_{50}$  were calculated by fitting the experimental data to equation 1: % Inhibition =  $100 \times (1 - V_i/V_0) = 100 [I]_0/(IC_{50} + [I]_0)$ , or equation 2: % Inhibition =  $100 [I]_0^{nH}/(IC_{50}^{nH} + [I]_0^{nH})$ , where  $V_i$  is the initial rate in the presence of the inhibitor,  $V_0$  is the initial rate in the absence of the inhibitor,  $[I]_0$  is the inhibitor concentration, nH is the Hill number (Figure 1).

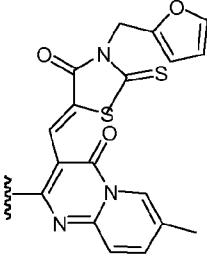
Figure 1 is illustrative of an inhibition curve obtained with compound 7 with respect to the CT-L activity.

The following table summarizes the results obtained for a selected series of piperazine derivatives of formula (I) as previously described.

15

| Cpd | Ar <sub>1</sub>                                                                     | R <sup>1</sup>                                                                                                                | Z                 | E represents $-(R^3)_q-(Ar_2)_r$ |                                                                                     |                                                              | IC <sub>50</sub> ( $\mu$ M) or % Inhibition (inhibitor concentration) on chymotrypsin-like activity | IC <sub>50</sub> ( $\mu$ M) or % Inhibition (inhibitor concentration) on post-acid activity | IC <sub>50</sub> ( $\mu$ M) or % Inhibition (inhibitor concentration) on trypsin-like activity |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|-------------------|----------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
|     | m = 1,<br>X : covalent bond                                                         |                                                                                                                               | t = 1             | R <sup>3</sup><br>q = 0          | Ar <sub>2</sub><br>r = 1                                                            | R <sup>2</sup>                                               |                                                                                                     |                                                                                             |                                                                                                |
| 1   |  | <i>p</i> -NO <sub>2</sub>                                                                                                     | S(O) <sub>2</sub> |                                  |  | <i>p</i> -CH <sub>2</sub> -CH(CH <sub>3</sub> ) <sub>2</sub> | 9.4 $\pm$ 1.2                                                                                       | 6.3 $\pm$ 1.6                                                                               | NI                                                                                             |
| 2   |  | <i>o</i> -CH <sub>3</sub> ,<br><i>m</i> -Cl                                                                                   | S(O) <sub>2</sub> |                                  |  | <i>p</i> -C(CH <sub>3</sub> ) <sub>3</sub>                   | 16.8 $\pm$ 2.1                                                                                      | 5.4 $\pm$ 1.2                                                                               | NI                                                                                             |
| 3   |  | <i>o</i> -NO <sub>2</sub> ,<br><i>p</i> -Cl                                                                                   | S(O) <sub>2</sub> |                                  |  | <i>p</i> -C(CH <sub>3</sub> ) <sub>3</sub>                   | 18.2 $\pm$ 3.3                                                                                      | 7.1 $\pm$ 2.2                                                                               | 17% (20 $\mu$ M)                                                                               |
| 4   |  | <i>p</i> NO <sub>2</sub> ,<br><br><i>m</i> | S(O) <sub>2</sub> |                                  |  | <i>p</i> -Cl                                                 | 24.2 $\pm$ 4.8                                                                                      | 20.2 $\pm$ 0.9                                                                              | NI                                                                                             |

|    |                                                                                     |                                                                                                                    |                 |               |                                                                                      |                                        |                            |                             |                                           |
|----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|-----------------|---------------|--------------------------------------------------------------------------------------|----------------------------------------|----------------------------|-----------------------------|-------------------------------------------|
| 5  |    | $p\text{-NO}_2$<br><br><i>m</i>   | $\text{S(O)}_2$ |               |     | $p\text{-CH}_3$                        | 22%<br>(50 $\mu\text{M}$ ) | 1.1 $\pm$ 0.1               | Activation<br>x4.6<br>(50 $\mu\text{M}$ ) |
| 6  |    | $p\text{-NO}_2$<br><br><i>m</i>   | $\text{S(O)}_2$ |               |     | $p\text{-Cl}$                          | 1.4 $\pm$ 0.3              | 9.2 $\pm$ 1.4               | Activation<br>x5.6<br>(50 $\mu\text{M}$ ) |
| 7  |    | $p\text{-NO}_2$<br><br><i>m</i>   | $\text{S(O)}_2$ |               |     | $p\text{-C(CH}_3)_3$                   | 10.6 $\pm$ 1.3             | NI                          | NI                                        |
| 8  |    | $p\text{-NO}_2$<br><i>m</i><br>   | $\text{S(O)}_2$ |               |     | $p\text{-NH-CO-CH}_3$                  | 60.0 $\pm$ 13.0            | 55%<br>(100 $\mu\text{M}$ ) | 77.0 $\pm$ 5.0                            |
| 9  |    | $p\text{-NO}_2$ , $m\text{-NH-CH}_2\text{-CH(CH}_3)_3$                                                             | $\text{S(O)}_2$ |               |     | $m\text{-O-CH}_3$<br>$p\text{-O-CH}_3$ | 73.0 $\pm$ 8.0             | NI                          | NI                                        |
| 10 |   | $p\text{-OCH}_3$                                                                                                   | $\text{C(S)}$   | NH            |    | $p\text{-NO}_2$                        | 10.8 $\pm$ 0.9             | 9.0 $\pm$ 1.2               |                                           |
| 11 |  | $p\text{-NO}_2$<br><i>m</i><br> | $\text{S(O)}_2$ | $\text{CH}_2$ |   | H                                      | 91.0 $\pm$ 7.0             | NI                          | NI                                        |
|    | <b>m = 1 and X represents</b><br><b>*-OCH<sub>2</sub>CO-□</b>                       |                                                                                                                    |                 | <b>q = 0</b>  | <b>r = 1</b>                                                                         |                                        |                            |                             |                                           |
| 12 |  | H                                                                                                                  | $\text{S(O)}_2$ |               |   | H                                      | 1.6 $\pm$ 0.1              | 2.3 $\pm$ 0.2               | NI                                        |
|    | <b>m = 0 and X represents -C(O)-Het<sub>2</sub></b>                                 |                                                                                                                    |                 | <b>q = 1</b>  |                                                                                      |                                        |                            |                             |                                           |
| 13 |  |                                                                                                                    | $\text{C(S)}$   | NH            |  | H                                      | 55 $\pm$ 7.8               | 42%<br>(100 $\mu\text{M}$ ) | 33%<br>(100 $\mu\text{M}$ )               |
| 14 | <b>m = 0 and X represents a -C<sub>1</sub>-C<sub>5</sub> alkylgroup</b>             |                                                                                                                    | <b>t = 0</b>    |               | <b>E represents</b>                                                                  |                                        |                            |                             |                                           |

|  |                                  |  |  |                                                                                    |        |                    |  |
|--|----------------------------------|--|--|------------------------------------------------------------------------------------|--------|--------------------|--|
|  | -CH <sub>2</sub> CH <sub>3</sub> |  |  |  | 13±1.5 | 55%<br>(100<br>μM) |  |
|--|----------------------------------|--|--|------------------------------------------------------------------------------------|--------|--------------------|--|

NI : No inhibition

The reversible property of the inhibition was demonstrated by abolishing the inhibition in the presence of an excess of substrate.

- 5 The inhibitors act selectively on proteasome with no inhibition at 100 μM of human calpain-I (for example, compounds 5 and 12).

### Example 2

#### **Effects on cell viability**

- 10 The cell survival was determined with the XTT assay. Human cells (HeLa from cervical carcinoma and HEK-293 from epithelial kidney) were obtained from Invitrogen (Cergy-Pontoise, France). The cells were grown at 37°C in DMEM supplemented with 10% fetal bovine serum (Invitrogen) in a humidified atmosphere of 5% CO<sub>2</sub> and 95% air.

- 15 5 x 10<sup>3</sup> cells in 100 μL culture medium were exposed for 48 h in 96-well plates to increasing concentrations of compounds: 5-100 μM, final concentration of DMSO is 1 % (v/v). The culture medium is then replaced by 100 μL of DMEM F12 culture medium devoid of phenol red and containing a mixture of XTT (0.3 mg/mL) and PMS (8.3 nM) (XTT: 2,3-bis[2-methoxy-4-nitro-5-sulfophenyl-2H-tetrazolium-5-carboxyanilide sodium; 20 PMS: phenazine methosulfate, both purchased from Sigma, Saint Quentin Fallavier, France). Cells were then incubated for 3 h at 37 °C.

During this incubation, the mitochondrial deshydrogenases of viable cells hydrolyzed the tetrazolium cycle of XTT, leading to orange formazan crystals soluble in aqueous solution.

- 25 The orange color was measured at 485 nm using a BMG Fluostar microplate reader.

In control experiments, cells were treated by the vehicle (DMSO) at the same concentration than that used for the inhibitors.

The cytotoxicity activity of drugs was expressed as the concentration inhibiting cell growth by 50% (EC<sub>50</sub>) calculated from the survival curves. The experimental data are fitted to the following equation, describing the relationship between % survival and drug concentration (C):

$$\% \text{ cell survival} = 100 - (E_{\max} \times C^n) / (C^n + EC_{50}^n)$$

where C is the drug concentration; E<sub>max</sub> is the maximum drug effect (%); EC<sub>50</sub> is the concentration that produces one-half of the maximum effect; and n is the Hill constant, which describes the shape of the curve.

For example, EC<sub>50</sub> ≈ 4.7 μM for compound 7 (HEK-293 cells) (Figure 2).

### Example 3

#### **Inhibition of proteasome in a cell assay**

In order to demonstrate that the cytotoxic effect observed on tumor cells results from the specific inhibition of cellular proteasome, the accumulation of ubiquitinated proteins was determined.

Indeed, if the proteasomes are inhibited, in particular the proteasome 26S, the degradation of ubiquitinated proteins should be blocked, and those proteins should accumulate.

240 000 HEK-293 cells were incubated for 16 h, in presence of piperazine derivatives at the concentration of 10 μM.

After extraction of the proteins (centrifugation of lysed cells), the concentration of proteins in the sample was determined with the BCA (Bicinchoninic Acid) protein Assay.

3 μg of proteins for each sample were deposited into a SDS-PAGE gel at 8%.

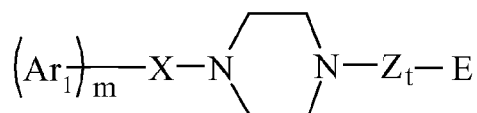
The Western blot with an anti-ubiquitin antibody shows an accumulation of ubiquitinated proteins.

The piperazine derivatives are observed, as MG132 (aldehyde inhibitor of the proteasome) to induce an accumulation of ubiquitinated proteins.

Therefore, the proteasome inhibitors of the invention effectively cross the cell membranes and inhibit the proteasome.

**CLAIMS**

1. Use of at least one piperazine derivative of formula (I):



wherein

5  $m = 0$  or  $1$ ,

$\text{Ar}_1$  representing a  $\text{C}_6\text{-C}_{10}$  aryl group, substituted with at least one R group, said R group being chosen among:

- H, or
- an halogen group, or
- 10 - a  $\text{NO}_2$  group, or
- an hydroxyl group, or
- a linear, branched or cyclic, saturated or unsaturated,  $\text{C}_1\text{-C}_5$  alkyl group optionally substituted with a  $\text{C}_6\text{-C}_{10}$  aryl group, or
- a linear, branched or cyclic, saturated or unsaturated,  $\text{C}_1\text{-C}_5$  aminoalkyl or
- 15 amidoalkyl group, or
- a linear, branched or cyclic, saturated or unsaturated,  $\text{C}_1\text{-C}_5$  alkoxy group, or
- a carbonyloxyalkyl group with said alkyl group being a linear, branched, saturated or unsaturated  $\text{C}_1\text{-C}_5$  alkyl group,
- $^*-(\text{A})_p-(\text{CH}_2)_n-\text{B}$

20 with  $^*$ - representing a covalent bond with  $\text{Ar}_1$ , A representing an heteroatom chosen among N, O or S or a carbonyl group,  $p = 0$  or  $1$ ,  $n$  representing an integer ranging from  $0$  to  $4$ , and B being chosen from  $\text{Het}_1$  or  $\text{Ar}_3$ :

- $\text{Het}_1$  representing a, saturated or unsaturated, 5-6 membered ring
- 25 comprising at least one heteroatom, optionally substituted with a  $\text{C}_6\text{-C}_{10}$  aryl group, said aryl group being optionally substituted with one or more  $\text{NO}_2$  group(s),



- Ar<sub>3</sub> representing a C<sub>6</sub>-C<sub>10</sub> aryl group optionally substituted with one or more linear, branched or cyclic, saturated or unsaturated C<sub>1</sub>-C<sub>5</sub> alkoxy group,

X represents:

5 when m = 1,

- a covalent bond, or  
 - \*-OCH<sub>2</sub>C(O)-□ with \*- representing a covalent bond with Ar<sub>1</sub> and -□ representing a covalent bond with the piperazine-derived radical, or

when m = 0,

10 - a linear, branched or cyclic, saturated or unsaturated, C<sub>1</sub>-C<sub>5</sub> alkyl group,

or

- -C(O)Het<sub>2</sub>, with Het<sub>2</sub> being as the above-defined Het<sub>1</sub> group,

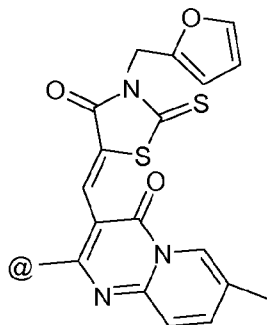
t = 0 or 1,

Z representing one group chosen among C(S), (CH<sub>2</sub>)<sub>b</sub> with b = 1 or 2, CH=CH, or

15 S(O)<sub>2</sub>,

E representing:

when t = 0,



@- representing a covalent bond with the piperazine-derived radical,

20 or

when t = 1

@-(R<sup>3</sup>)<sub>q</sub>-(Ar<sub>2</sub>)<sub>r</sub>,

with

@- representing a covalent bond with Z, q and r representing,

25 independently of each other, 0 or 1,

when r = 1, R<sup>3</sup> representing a linear or branched, saturated or unsaturated

C<sub>1</sub>-C<sub>5</sub> alkylene group optionally incorporating at least one heteroatom chosen among N, O

or S, or being an heteroatom chosen among N, O or S, or when r represents 0, R<sup>3</sup> being a linear, branched or cyclic, saturated or unsaturated, C<sub>1</sub>-C<sub>5</sub> alkyl group, optionally substituted with an hydroxyl, an amino or a thiol group,

Ar<sub>2</sub> representing, when m = 0, a 5-6 membered heteroaryl group, or when  
5 m = 1, a C<sub>6</sub> aryl or a 5-6 membered heteroaryl group, said aryl or heteroaryl group being substituted with at least one R group, said R group being as above-defined, or a pharmaceutically acceptable salt thereof, as proteasome activity modulator for the preparation of a pharmaceutical composition intended to prevent and/or treat a disease condition mediated by the proteasome activity.

10 2. The use according to the preceding claim, wherein Ar<sub>1</sub> is substituted with at least two R<sup>1</sup> groups, identical or different, said R<sup>1</sup> groups being as the R group above-defined.

3. The use according to claim 2, wherein R<sup>1</sup> is chosen among:

-H, or

15 - Cl or Br, or

- NO<sub>2</sub>, or

- a linear, branched or cyclic, saturated or unsaturated C<sub>2</sub>-C<sub>4</sub> alkyl group, in particular a methyl, an ethyl, a propyl, an iso-propyl, a n-butyl, an iso-, a sec- or a tert-butyl group, and more particularly a methyl, an ethyl or an iso-propyl group, or

20 - a linear, branched or cyclic, saturated or unsaturated C<sub>2</sub>-C<sub>4</sub> aminoalkyl group, in particular an aminomethyl, an aminoethyl, an aminopropyl, an iso-aminopropyl, a n-aminobutyl, an iso-, a sec- or a tert-aminobutyl group, or

- a linear, branched or cyclic, saturated or unsaturated C<sub>2</sub>-C<sub>4</sub> alkoxy group, in particular a methoxy, an ethoxy, a propoxy, an iso-propoxy, a n-butoxy, an iso-, a sec- or a  
25 tert-butoxy group,

-  $^{*}-(A)_p-(CH_2)_n-B$ , with  $^{*}$ - being as above-defined, A being N, S, or C(O), n ranging from 0 to 3, and in particular from 1 to 2, and B being Het<sub>1</sub> or Ar<sub>3</sub>:

- Het<sub>1</sub> representing a saturated or unsaturated heterocyclic group comprising at least one heteroatom chosen among oxygen, sulfur and  
30 nitrogen, optionally substituted with one or more NO<sub>2</sub> group(s), or

- Ar<sub>3</sub> representing a phenyl or a naphthyl group, in particular a phenyl group, optionally substituted with an alkoxy group as above-defined.

4. The use according to anyone of the preceding claims, wherein Ar<sub>1</sub> is chosen among a phenyl group or a naphthyl group, and in particular is a phenyl group .

5. The use according to the preceding claim, wherein when said R<sup>1</sup> group(s) represent(s) an electronegative functional group and Ar<sub>1</sub> is a phenyl group, said R<sup>1</sup> group(s) may be in position *meta* and/or *para* of Ar<sub>1</sub> with respect to the X moiety, and/or when said R<sup>1</sup> group(s) represent(s) an electropositive group and Ar<sub>1</sub> is a phenyl group, said R<sup>1</sup> group(s) may be in position *ortho* and/or *para* of Ar<sub>1</sub> with respect to the X moiety.

6. The use according to anyone of the preceding claims, wherein E represents @-(R<sup>3</sup>)<sub>q</sub>-(Ar<sub>2</sub>)<sub>r</sub> with Ar<sub>2</sub> being substituted with at least two R<sup>2</sup> groups, identical or different, said R<sup>2</sup> group being as the R group above-defined.

7. The use according to the preceding claim, wherein R<sup>2</sup> is chosen among:

- H, or

- Cl or Br, or

- a linear, branched or cyclic, saturated or unsaturated, C<sub>2</sub>-C<sub>4</sub> alkyl group, in particular a methyl, an ethyl, a propyl, an iso-propyl, a n-butyl, an iso-, a sec- or a tert-butyl group, or

- a linear, branched or cyclic, saturated or unsaturated, C<sub>2</sub>-C<sub>4</sub> alkoxy group, in particular a methoxy, an ethoxy, a propoxy or an iso-propoxy group, a n-butoxy, an iso-, a sec- or a tert-butoxy group, or

- a linear, branched or cyclic, saturated or unsaturated, C<sub>2</sub>-C<sub>4</sub> amidoalkyl group, in particular an amidomethyl, an amidoethyl, an amidopropyl or an amido-iso-propyl group, an amido-n-butyl, an-amido-iso-, an amido-sec- or an amido-tert-butyl group or

- a carbonyloxyalkyl group with said alkyl group being a linear, branched, saturated or unsaturated C<sub>2</sub>-C<sub>4</sub> alkyl group, in particular being a methyl, an ethyl or a propyl group.

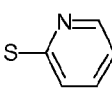
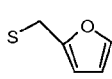
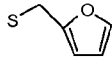
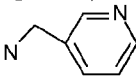
8. The use according to anyone of the preceding claims, wherein said Ar<sub>2</sub> is a phenyl group, a pyridine group, or a thiophen group, and in particular is a phenyl group.

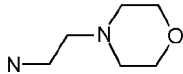
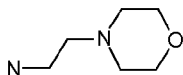
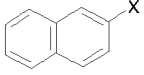
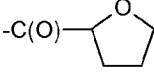
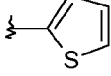
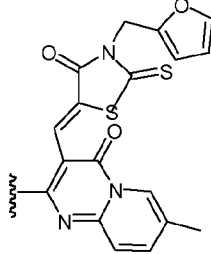
9. The use according to the preceding claim, wherein when said R<sup>2</sup> group represents an electronegative functional group and Ar<sub>2</sub> is a phenyl group, said R<sup>2</sup> group may be in position *para* of Ar<sub>2</sub> with respect to the -Z<sub>t</sub>-(R<sup>3</sup>)<sub>q</sub> moiety, and/or when said R<sup>2</sup>

group(s) represent(s) an electropositive group and Ar<sub>2</sub> is a phenyl group, said R<sup>2</sup> group(s) may be in position *meta* and/or *para* of Ar<sub>2</sub> with respect to the -Z-(R<sup>3</sup>)<sub>q</sub> moiety.

10. The use according to anyone of the preceding claims, wherein when r represents 0, R<sup>3</sup> represents an hydroxyalkyl ranging from C<sub>2</sub> to C<sub>4</sub>, and in particular is an hydroxy methyl, an hydroxy-1-ethyl, an hydroxyl-2-ethyl or an hydroxyl-3 propyl group.

11. The use according to anyone of the preceding claims, wherein m, Ar<sub>1</sub>, R<sup>1</sup>, X, Z, t, E, R<sup>3</sup>, Ar<sub>2</sub>, R<sup>2</sup>, q and r are as defined in the following table:

|   | Ar <sub>1</sub>                                                                     | R <sup>1</sup>                                                                                                                 | Z                 | E represents -(R <sup>3</sup> ) <sub>q</sub> -(Ar <sub>2</sub> ) <sub>r</sub> |                                                                                       |                                                                  |
|---|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|-------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------------------------------------|
|   |                                                                                     |                                                                                                                                |                   | R <sup>3</sup><br>q = 0                                                       | Ar <sub>2</sub><br>r = 1                                                              | R <sup>2</sup>                                                   |
|   | m = 1 ; X :<br>covalent<br>bond                                                     |                                                                                                                                | t = 1             |                                                                               |                                                                                       |                                                                  |
| 1 |    | <i>p</i> -NO <sub>2</sub>                                                                                                      | S(O) <sub>2</sub> |                                                                               |    | <i>p</i> -CH <sub>2</sub> -<br>CH(CH <sub>3</sub> ) <sub>2</sub> |
| 2 |   | <i>o</i> -CH <sub>3</sub> ,<br><i>m</i> -Cl                                                                                    | S(O) <sub>2</sub> |                                                                               |  | <i>p</i> -C(CH <sub>3</sub> ) <sub>3</sub>                       |
| 3 |  | <i>o</i> -NO <sub>2</sub> ,<br><i>p</i> -Cl                                                                                    | S(O) <sub>2</sub> |                                                                               |  | <i>p</i> -C(CH <sub>3</sub> ) <sub>3</sub>                       |
| 4 |  | <i>p</i> NO <sub>2</sub> ,<br><br><i>m</i>  | S(O) <sub>2</sub> |                                                                               |  | <i>p</i> -Cl                                                     |
| 5 |  | <i>p</i> -NO <sub>2</sub> ,<br><br><i>m</i> | S(O) <sub>2</sub> |                                                                               |  | <i>p</i> -CH <sub>3</sub>                                        |
| 6 |  | <i>p</i> -NO <sub>2</sub> ,<br><br><i>m</i> | S(O) <sub>2</sub> |                                                                               |  | <i>p</i> -Cl                                                     |
| 7 |  | <i>p</i> -NO <sub>2</sub> ,<br><br><i>m</i> | S(O) <sub>2</sub> |                                                                               |  | <i>p</i> -C(CH <sub>3</sub> ) <sub>3</sub>                       |
| 8 |  | <i>p</i> -NO <sub>2</sub> ,<br><i>m</i>                                                                                        | S(O) <sub>2</sub> |                                                                               |  | <i>p</i> -NH-CO-CH <sub>3</sub>                                  |

|    |                                                                                     |                                                                                                                              |                   |                 |                                                                                       |                                                           |
|----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|-------------------|-----------------|---------------------------------------------------------------------------------------|-----------------------------------------------------------|
|    |                                                                                     |                                             |                   |                 |                                                                                       |                                                           |
| 9  |    | <i>p</i> -NO <sub>2</sub> , <i>m</i> -NH-CH <sub>2</sub> -CH(CH <sub>3</sub> ) <sub>3</sub>                                  | S(O) <sub>2</sub> |                 |    | <i>m</i> -O-CH <sub>3</sub> , <i>p</i> -O-CH <sub>3</sub> |
|    |                                                                                     |                                                                                                                              |                   | <b>q = 1</b>    |                                                                                       |                                                           |
| 10 |    | <i>p</i> -OCH <sub>3</sub>                                                                                                   | C(S)              | NH              |    | <i>p</i> -NO <sub>2</sub>                                 |
| 11 |    | <i>p</i> -NO <sub>2</sub> ,<br><i>m</i><br> | S(O) <sub>2</sub> | CH <sub>2</sub> |    | H                                                         |
|    | <b>m = 1 and X represents *-OCH<sub>2</sub>CO-□</b>                                 |                                                                                                                              |                   | <b>q = 0</b>    | <b>r = 1</b>                                                                          |                                                           |
| 12 |    | H                                                                                                                            | S(O) <sub>2</sub> |                 |   | H                                                         |
|    | <b>m = 0 and X represents -C(O)-Het<sub>2</sub></b>                                 |                                                                                                                              |                   | <b>q = 1</b>    |                                                                                       |                                                           |
| 13 |  |                                                                                                                              | C(S)              | NH              |  | H                                                         |
|    | <b>m = 0 and X represents a C<sub>1</sub>-C<sub>5</sub> alkyl group</b>             |                                                                                                                              | <b>t = 0</b>      |                 | <b>E represents</b>                                                                   |                                                           |
| 14 | -CH <sub>2</sub> CH <sub>3</sub>                                                    |                                                                                                                              |                   |                 |  |                                                           |

12. The use according to anyone of the preceding claims, wherein said disease condition is chosen among cancers, immunological diseases, auto-immune diseases, allograft rejections, viral diseases, such as mumps, measles, Rous sarcoma, AIDS, parasitic diseases, such as malaria or trypanosome, bacterial infections, such as tuberculosis, inflammatory diseases, such as polyarthritis or liver inflammation, cardiac diseases and ischemic strokes, such as myocardial, cerebral or pulmonary ischemic injuries, muscular

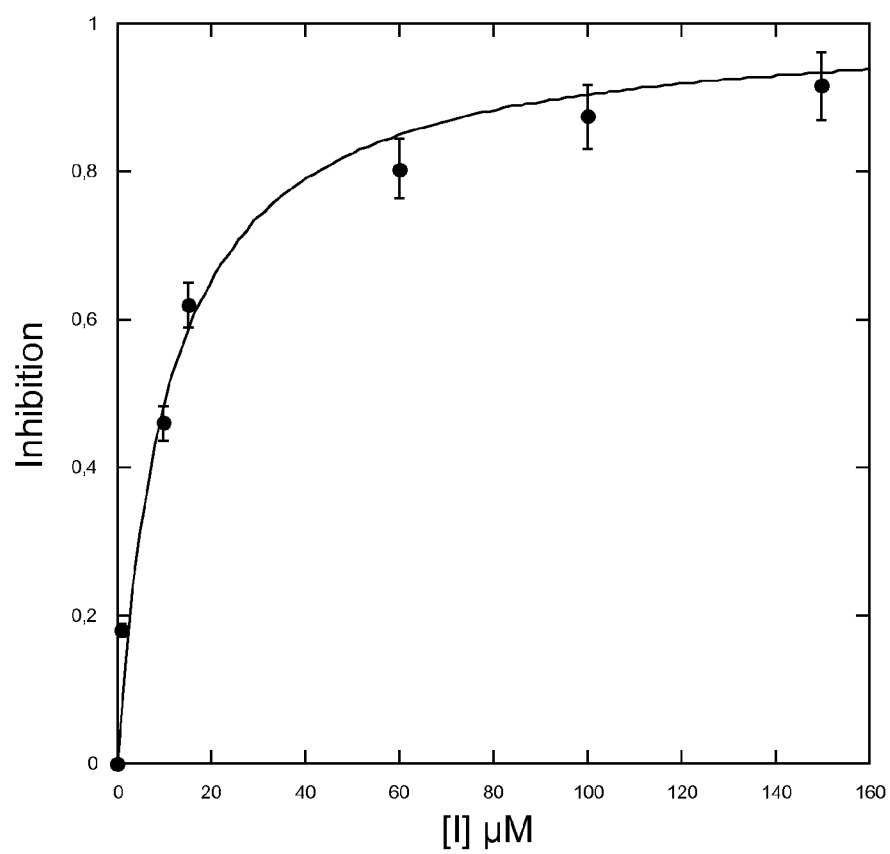
dystrophies, muscle wasting, traumatisms, burns, disease conditions associated with aging, such as neurodegenerative diseases.

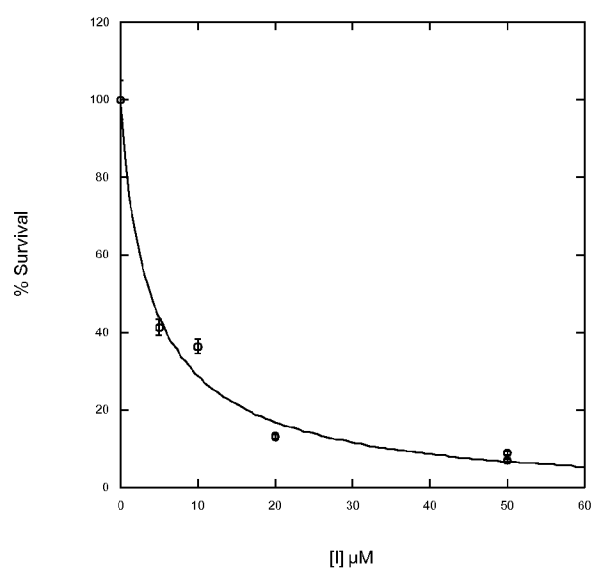
13. Use of at least one effective amount of at least one piperazine derivative as defined according to anyone of claims 1 to 11 as active agent in a cosmetic composition  
5 for the prevention and/or treatment of skin aging.

14. Kit-of-parts comprising (i) at least one piperazine derivative as defined according to anyone of claims 1 to 11 and (ii) at least one agent useful for the prevention and/or the treatment of a cancer condition, said agent being different of said piperazine derivative (i).

- 10 15. A piperazine derivative according to anyone of claims 1 to 11 for use as a medicament.

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**FIGURE 1**

**FIGURE 2**



# INTERNATIONAL SEARCH REPORT

International application No  
PCT/IB2009/052919

## A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/4965 A61K31/497 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                             | Relevant to claim No. |
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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

\* Special categories of cited documents:

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- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

8 October 2009

Date of mailing of the international search report

16/10/2009

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Authorized officer

Damiani, Federica

# INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2009/052919

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                            | Relevant to claim No. |
|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
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|           | -----                                                                                                                                                                                                                                                                                                                                                                         |                       |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2009/052919

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s)                                                                                                                                                                                               | Publication<br>date                                                                                                                                                                |
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